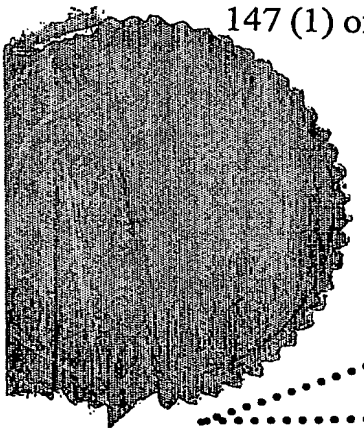
PCT / IN 03 / 0 0 2 4 1

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and provisional specification filed on 16.07.2002 in respect of Patent Application No. 648/MUM/2002 of Cadila Healthcare Limited, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380015, Gujarat, India.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.



Dated this 01 day of August 2003

M.A. Haafeez

(M.A. HAAFEEZ)
ASST. CONTROLLER OF PATENTS & DESIGNS

PRIORITY DOCUMENT
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FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT
(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, CADILA HEALTHCARE LIMITED, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare –

(a) That we are in possession of an invention titled

'A Novel Process To Prepare Pioglitazone *via* Several Novel Intermediates'

(b) That the Provisional Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that true and first inventor for the said invention is ,

(a) **Bipin PANDEY**, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Tower, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(b) **Vidya Bhushan LOHRAY**, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Tower, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(c) **Braj Bhushan LOHRAY**, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Tower, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: NIL

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
Patent and Trademark Attorneys
E 556, Greater Kailash II,
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Phone: 91 11 628 5603, 628 6012, 628 6025
Fax: 91 11 628 6005
Email: sna@vsnl.com

648/mum/2002
16/7/2002

648/मुंबई/2002

(7) Following declaration was given by the inventor

We, Bipin PANDEY, Vidya Bhushan LOHRAY and Braj Bhushan LOHRAY, all Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Tower, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India,

and the true and first inventors for this invention declare that the applicants herein are our assignees.

Bipin PANDEY

Vidya Bhushan LOHRAY

Braj Bhushan LOHRAY

(8) That to the best of our knowledge, information and belief the facts and matte rs stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

(9) Following are the attachments with this application:

(a) Provisional specification in triplicate
(b) Statement and Undertaking on FORM 3 in duplicate
(c) Power of Authority
(d) Form 2 in triplicate
(e) Power of Authority
(f) Abstract

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No..... ..... dated.....on ....Bank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 15th day of July , 2002

The Controller of Patents
The Patent Office,
At Mumbai

for CADILA HEALTHCARE LIMITED
(Dr. Braj Bhushan Lohray, President
Zydus Research Centre)

ZRC-NIPR-008

Form-2

THE PATENTS ACT, 1970

(39 OF 1970)

PROVISIONAL SPECIFICATION

A Novel Process To Prepare Pioglitazone *via* Several Novel Intermediates.

Cadila Healthcare Ltd.,

'Zydus Tower',

Satellite Cross Roads,

Gandhinagar – Sarkhej Highway,

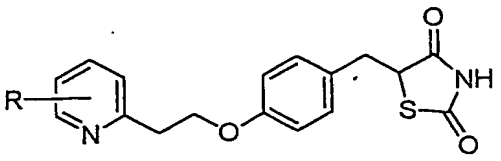
Ahmedabad – 380 015, Gujarat, India.

The following specification describes the nature of the invention:

Field of invention:

The present invention relates to a novel process for the production of various pyridine substituted 5-[4-[2-(alkyl substituted pyridyl)ethoxy]benzyl-2,4-thiazolidinedione derivatives of general formula 1, and their pharmaceutically acceptable salts.

Such compounds are known to exhibit hypoglycemic and hypolipidemic activities. The present invention also relates to the novel intermediates of formula 3, 5, 6, 8, 9, 13, 14 (Scheme I, II, III) and their corresponding salts, used either as a racemate or in optically pure form to prepare compounds of general formula 1. This invention, in particular, relates to a novel process for the production of 5-[4-[2-(5-ethyl-pyridyl)ethoxy]benzyl-2,4-thiazolidinedione (Pioglitazone hydrochloride, R in 1 is 5-ethyl).



1

Background of the invention:

The present invention provides a process to prepare various pyridine substituted 5-[4-[2-(alkyl substituted pyridyl)ethoxy]benzyl-2,4-thiazolidinedione derivatives of general formula 1, and their pharmaceutically acceptable salts. These compounds have been found to be advantageous for their therapeutic applications eg. antidiabetic and hypolipidemic, especially as insulin sensitizing agents. Such compounds have been described in patents US 4687777 and EP 193256. EP 0508740 discloses Pyridine N-oxide analogues of thiazolidinedione derivatives, including the N-oxide of Pioglitazone (1), having antidiabetic and hypolipidemic activity. US Patent No. 4444779 and EP 008203 discloses new thiazolidinedione compounds, including ciglitazone and their pharmaceutically acceptable salts thereof, which have similar antidiabetic properties.

Methods for production of various thiazolidinedione derivatives are described in US 4687777; Drugs of Future 15,1080(1990); Chemical and Pharmaceutical Bulletin 30, 3563(1982); 30, 3580(1982) and 32, 2267(1984). These methods invariably comprise low temperature diazotisation, condensation with lachrymetric and prone to polymerization

reagent acrylic ester in the presence of a copper catalyst by Meerwein arylation reaction to give a haloester, reacting it with thiourea to give an iminothiazolidine and finally hydrolyzing the same to get the required thiazolidinedione derivative. These methods include multistep synthetic processes and sometimes it is difficult to control Meerwein reaction at industrial scale, since it is an exothermic run-away type of reaction accompanied by the generation of a large amount of nitrogen gas, which is difficult to handle. Moreover, due to byproduct formation, purification becomes cumbersome. Besides, special measures are required in the Meerwein reaction for elimination of an extremely bad odour of acrylic acid ester, which must be used in excess. The disposal of excess material, along with heavy metals, requires additional effluent treatment protocols. These issues make the known route disadvantageous both technically and commercially.

Subsequently, new synthetic strategies have been reported in EP 0257781, which might lead to side product(s) eg. 2-vinyl-5-ethyl pyridine from tosylates, and require high pressure Raney Ni conversion of cyanide to formyl group. In an yet another invention, microbial reductase has been employed to obtain pharmaceutically active thiazolidine derivatives (WO 9310254).

Recently, Pioglitazone oxygenated metabolites have been patented (WO 9322445) as potentially useful compounds for the treatment of diabetes and as insulin sensitizing agents (J. Med. Chem., 1996, 39, 5053). PCT Patent No. WO 93/13095 describes the use of cobalt ion, a ligand and a reducing agent to convert the final step reduction of 5-methylene thiazolidinedione to saturated analogues.

US 5594015 describes the new use of Pioglitazone for the treatment of Psoriasis. Various other strategies to synthesize Pioglitazone are disclosed in Patents EP 0506273. As discussed above in the prior art, the known method to prepare compounds of general formula 1, in particular, Pioglitazone, involves technically difficult procedures to handle bad odour, low temperature diazotization, evolution of large excess of gas and special precautions to handle effluents.

Besides, above mentioned procedures lead to the formation of unwanted impurities, the removal of which is a time consuming process. Environmentally also, it requires evolution of HBr gas, which requires upstream processing and consequent additional cost.

Objective of the invention

The present inventors have examined possibilities to find out processes to overcome the above drawbacks. The main objective of the present invention is to provide novel processes for the manufacture of various pyridine substituted 5-[4-[2-(alkyl substituted pyridyl)ethoxy]benzyl-2,4-thiazolidinedione derivatives, especially Pioglitazone hydrochlorides (1, R = 5-ethyl). Another objective of the present invention is to report several new and novel intermediates for the manufacture of Pioglitazone hydrochloride.

Above objectives as well as other objectives and advantages of the present invention will become apparent to those skilled in the art, as we go through the following description, especially summary of the invention.

Summary of the invention

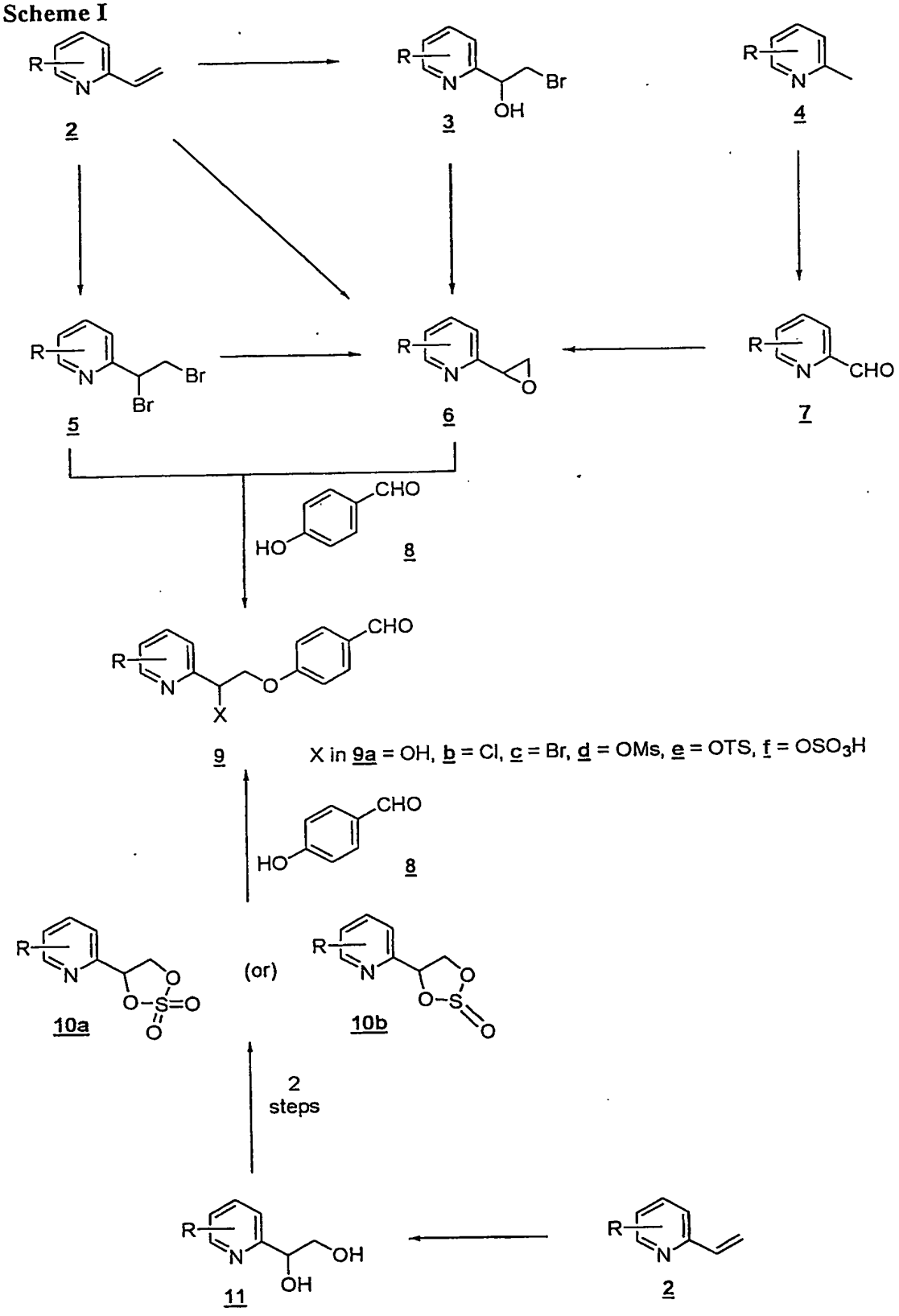
Accordingly, the present invention provides a new, novel and general process to prepare various pyridine substituted 5-[4-[2-(alkyl substituted pyridyl)ethoxy]benzyl-2,4-thiazolidinedione derivatives of general formula 1, and their pharmaceutically acceptable salts. The present invention especially provides a novel process to prepare Pioglitazone hydrochloride, *via* novel intermediates. This process involves lesser number of steps and uses novel intermediates. Some of the novel intermediates described in this invention are 3, 5, 6, 8, 9, 13 and 14.

Another objective of the present invention is to describe a process for an advanced intermediate 13 g R=3-ethyl, X=H (Scheme II) for Pioglitazone hydrochloride 1.

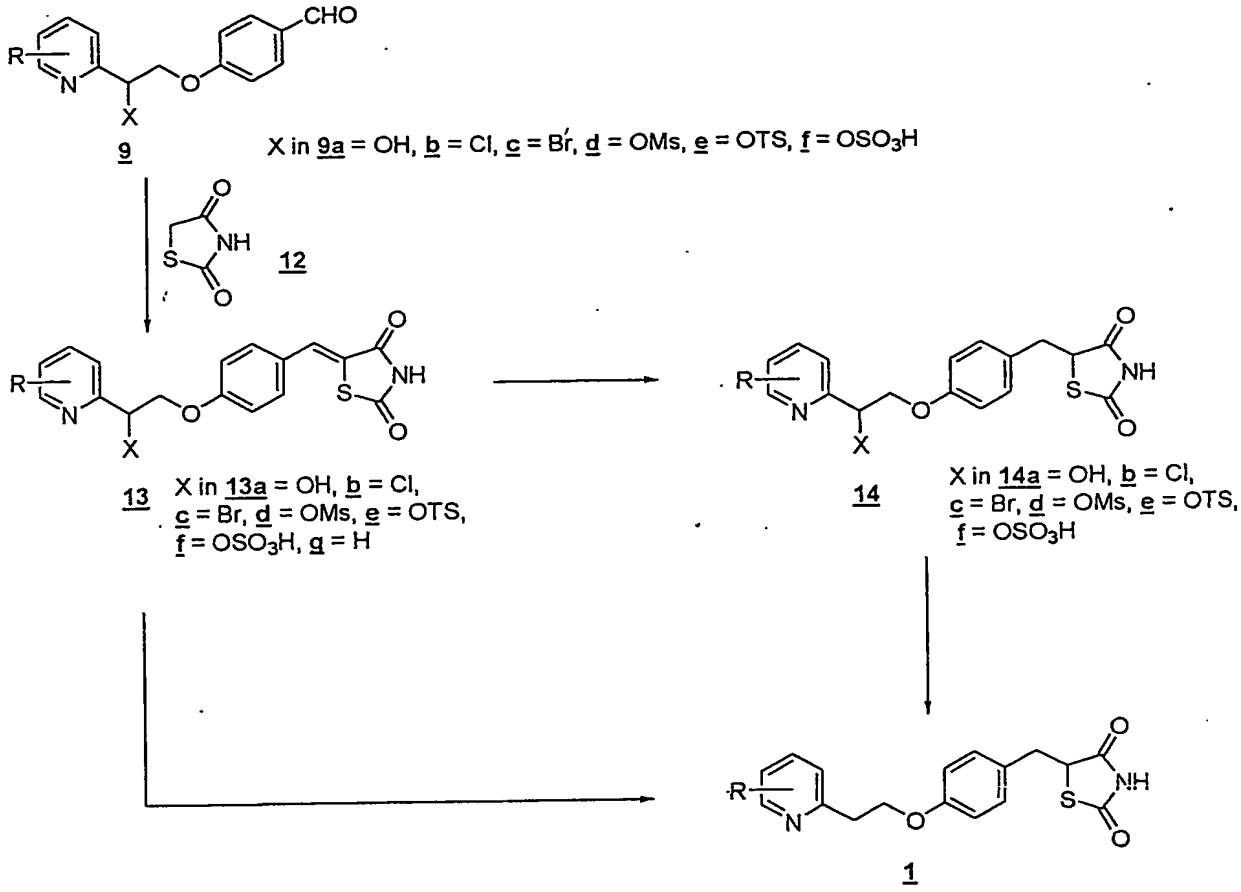
The most preferred objective of the present invention is to describe a process for the manufacture of Pioglitazone1 (R = 3-ethyl), and its pharmaceutically acceptable salts.

The preferred method to prepare 1 involves the synthetic sequence 2 to 9 to 13 to 14 to 1 and/or 2 to 9 to 13 to 1.

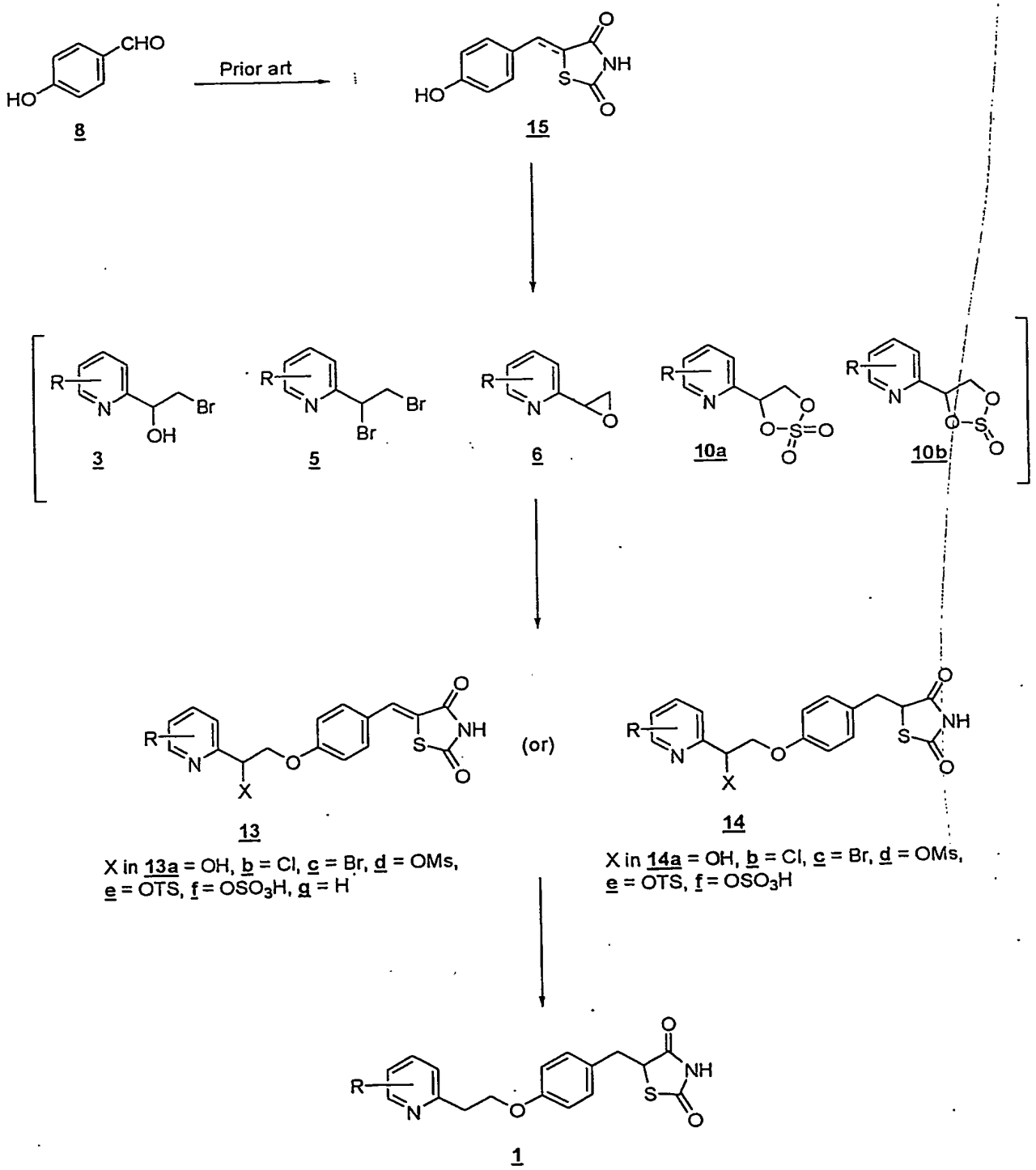
Scheme I


R
N
2
Br
OH
3
4
Br
Br
5
O
6
CHO
7
CHO
HO
8
CHO
X
9
X in 9a = OH, b = Cl, c = Br, d = OMs, e = OTS, f = OSO3H
CHO
HO
8
(or)
10a
10b
2
steps
OH
OH
11
2

Scheme II


CHO
R
N
O
X
9
X in 9a = OH, b = Cl, c = Br, d = OMs, e = OTS, f = OSO3H
NH
S
O
12
13
X in 13a = OH, b = Cl,
c = Br, d = OMs, e = OTS,
f = OSO3H, g = H
14
X in 14a = OH, b = Cl,
c = Br, d = OMs, e = OTS,
f = OSO3H
1

Scheme III



Detailed description of the invention

The present invention provides a novel process to prepare substituted 5-[4-[2-(alkyl substituted pyridyl)ethoxy]benzyl-2,4-thiazolidinedione derivatives of general formula 1, and their pharmaceutically acceptable salts. Referring to the general formula 1, where R is denoted by straight chain or branched alkyl group of one to six carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pentyl, *iso*-pentyl, neo-pentyl, hexyl etc, more preferably the lower alkyl groups of one to three carbon atoms. Such an alkyl group may be substituted in any position of the pyridine ring. The most preferred substituent and position for R in pyridine is 5-ethyl for Pioglitazone 1.

The starting materials, 2-vinyl-5-ethyl pyridine 2 (R = 5-ethyl, Scheme 1) and 5-ethyl-pyridine-2-carboxaldehyde (7, R = 5-ethyl), required for carrying out the multistep synthetic operations involved with this invention are known compounds, which may be easily prepared from commercially available 5-ethyl-2-pyridyl-2-ethanol or 5-ethyl-2-methyl pyridine, by those skilled in the art, using conventional methods.

The synthetic sequence comprises involvement of several novel intermediates eg. 9, 13, 14, 3, 6, 5, 10a and 10b with possibilities of varied substituents in 9, 13 and 14 (X = OH, Cl, Br, OTs, OMs, SO_3H) (Scheme I, II & III). Many of these novel intermediates eg. 9, 13 and 14 are inter convertible. For example, 9a(X=OH) which can be converted into 9b(X=Cl) or to 9d(X=OMs) or to 9e(X=OTs). The most preferred synthetic strategy to prepare 1 involves the synthetic sequence 2 to 9 to 13 to 14 to 1 (Scheme I/II) and/or 2 to 9 to 13 to 1.

The synthesis of novel key intermediate 9 with various substitution patterns eg. 9aX=OH, 4-[2-hydroxy-2-[5-ethyl-pyridyl]ethoxy benzaldehyde; 9bX=Cl, 4-[2-chloro-2-[5-ethyl-pyridyl]ethoxy benzaldehyde; 9cX=Br, 4-[2-bromo-2-[5-ethyl pyridyl] ethoxybenzaldehyde; 9dX=OMs, 4-[2-mesyl-2-[5-ethyl pyridyl]ethoxybenzaldehyde; 9eX=OTs, 4-[2-*p*-tosyl-2-[5-ethyl pyridyl]ethoxybenzaldehyde; 9fX=OSO_3H 4-[2-hydroxy sulfonyloxy-2-[5-ethyl pyridyl] ethoxybenzaldehyde etc, can be achieved by reacting *p*-hydroxy benzaldehyde with suitable inorganic base and suitable electrophiles

eg. bromohydrin 3, epoxide 6, or dibromide 5, or cyclic sulfate 10a, or cyclic sulfite 10b, in suitable solvents. Suitable inorganic bases include but are not limited to sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride, and the like. Suitable polar and neutral solvents for the above transformation include but are not limited to dimethyl sulfoxide, dimethyl formamide, tetrahydrofuran, dimethoxyethane, acetonitrile, toluene, and the like, in a ratio 3 to 50 volume with respect to the starting material. Phase transfer catalysis conditions may also be employed for better yield and quality. Many of the references described in R. C. Larrock, "Comprehensive Organic Transformations", John Wiley & Sons, Inc, 1999, 2nd Ed, page no's and references therein (herein referred to as Larrock's book) may be advantageously employed so long as it does not exert any undesirable effect on the main synthetic transformation. Alternatively, 2 can be reacted to 8 in one step to give 9cX=Br, *via* some of the synthetic transformations described in Larrock's book p. 642. Preferably, use of N-bromosuccinamide with 2,in the presence of 8, in an inert solvent can give 9cX=Br. Similarly, use of N-chloro-succinimide can lead to 9bX=Cl in one step.

Several methods are described for formation of bromohydrin 3 from olefins, Larrock's book p 640, 641 and 922, which can be exploited for vinyl pyridine 2. Suitable methods involve use of N-bromosuccinimide (1 to 3 eq) in a suitable solvent in the presence of atleast one equivalent of water. Suitable solvents for bromohydrin 3 formation are dimethyl sulfoxide, acetone, tetrahydrofuran, *tert*-butanol, dimethoxyethane in a ratio of 3 to 50 volume. Treatment of base K_2CO_3 with bromohydrin 3 gives the corresponding epoxide 6. Alternatively, one can form epoxide 6 directly from olefin 2, as per various methods described in Larrock's book p 916 to 920, or *via* reaction of Corey's ylide *(J. Am. Chem. Soc. 1965, 87, 1353)* (trimethyl sulfonium methylylide) with aldehyde 1.

Bromination of olefin 2 with bromine in a neutral solvent can give 5, *via* the several procedures reported in Larrock's book p 632-633. Similarly, cyclic sulfate 10a may be prepared *via* oxidation of cyclic sulfite10b, which in turn may be obtained form diol 11 by reacting with thionyl chloride, Larrock's book 972-973. The formation of diol 11, from olefin 2, can be accomplished, in a similar way by several procedures reported in

Larrock's book p 996-1001. In all the above transformations (Scheme I) upon completion of the reaction, the desired compound is easily isolated from the reaction mixture in a most conventional manner eg. extracting in organic layer, washing with water, drying organic layer, concentrating and purifying/crystallizing the desired final product.

As mentioned earlier, some of the substituents in 9, are interconvertible. Thus, alcohol 9aX=OH, may be transformed to chloride 9bX=Cl by reacting with thionyl chloride in an inert solvent. Similarly, bromide 9cX=Br, can be obtained by treating alcohol 9aX=OH with PBr_3. Tosylation (9eX=OTs) of alcohol 9aX=OH, is achieved by reacting with TosCl (*p*-toluene sulfonyl chloride) in the presence of an organic or inorganic base. Similarly, mesylated compound 9dX=OMs, may be prepared by reacting alcohol 9aX=OH with mesyl chloride (methane sulfonyl chloride) in the presence of a base. Such transformations are of common knowledge to the people skilled in the art and the literature for such reactions are available in popular text books eg. Larrock's book p 692-700. Similarly 9f X=OSO_3H can be hydrolysed to 9aX=OH by treatment with alkali metal hydroxides eg. NaOH, KOH, LiOH, etc.

The condensation of variously substituted aromatic aldehyde 9a-e with 2,4-thiazolidinedione 12 is accomplished by azeotropic removal of water in a suitable solvent and in the presence of an organic base and catalytic amount of organic acid. Suitable organic bases include, but are not limited to ammonia, methyl amine, ethyl amine, *n*-butyl amine, pyrrolidine, piperidine, pyridine, morpholine, piperazine, diethylamine, di-isopropyl amine, triethyl amine and the like; whereas suitable catalytic acids include, but are not limited to acetic acid, *p*-tolune sulfonic acid , hydrochloric acid, hydrobromic acid and the like. Suitable organic solvents for such condensation include, but are not limited to methanol, ethanol, propanol, 2-propanol, butanol, *iso*-butanol, 2-methoxyethanol, dimethyl formamide, dimethyl sulfoxide, sulfolane, acetonitrile, dioxalane, dimethoxyethane, toluene, acetic acid and the like. Similar condensation of active methylenes with aldehyde(s)/ketone(s) are also reported in Larrock's book p 317-325, with varying experimental conditions.

The chemoselective reduction of 13a-e (X=OH, Cl, Br, OMs, OTs) to 14a-e (X=OH, Cl, Br, OMs, OTs) is accomplished by usual double bond reducing methodologies described in Larrock's book p 7-8. In particular, conversion of 13a(X=OH) to 14a(X=OH) is achieved by reducing with metal borohydrides in a suitable solvent, in the presence of a cobalt catalyst and a ligand. Suitable solvents, in the present invention, include but are not limited to methanol, ethanol, *iso*-propanol, acetone, dimethyl formamide (DMF) and tetrahydrofuran. Suitable cobalt catalyst include $CoCl_2$ (Cobaltous chloride), $Co(OAc)_2$ (Cobaltous acetate) or $CoCl_3$ (Cobaltic chloride). Some of the ligands useful for this transformation are 2,2'-bipyridyl, 1,10-phenanthroline and dimethyl glyoxime. Sodium borohydride is the preferred reducing agent, but other borohydrides such as lithium borohydride, potassium borohydride, tetraalkylammonium borohydride or Zinc borohydride can also be used.

Alternatively, chemoselective reduction of 13 to 14 is accomplished under catalytic reduction conditions in a suitable solvent in the presence of a suitable catalyst. Suitable solvents include but are not limited to alkanols such as methanol, ethanol, propanol etc; ethers such as dioxane, dimethoxyethane, tetrahydrofuran, and other miscellaneous solvents eg. ethyl acetate, acetic acid, dimethyl formamide, N-methyl pyrrolidine, either alone or in combinations thereof. Suitable catalysts employed in this transformation include, but are not limited to palladium black, palladium charcoal, palladium on barium sulfate, palladium on barium carbonate, platinum oxide, platinum on carbon, and the like.

By varying experimental conditions in the above two reducing conditions eg. alkali metal borohydrides and catalytic hydrogenation conditions, the transformation from 13 to 14 and finally 14 to 1 may be accomplished in one step, especially if the substituents in 13 are X = Cl, Br, OTs, OMs. Usually, 3 to 10 molecular equivalents of metal borohydrides mentioned above, and high reflux temperature are required to accomplish both transformations in one step.

For deoxygenation of 13a or 14a (X=OH), to 1(X=H), triethyl silane induced reduction in the presence of a suitable protic acids are advantageous. Some of the protic acids used include, but are not limited to conc. sulfuric acid, acetic acid, triflic acid, Nation-H, trifluoroacetic acid and the like. There are several other useful methods described in

Larrock's book p 44-45, to accomplish similar transformations and any one of them may be advantageously used, so long as they achieve our objectives.

The transformation of 14b-e (X = Cl, Br, OMs, OTs) to 1 may also be achieved by reacting with zinc in acetic acid under reflux conditions, in a suitable solvent (Larrock's book 47-49, 52).

Alternatively, the useful intermediates 13a-f or 14a-g may also be obtained by reacting the key intermediates 3, 5, 6, 10a and 10b with another advanced intermediate unsaturated benzylidene type 15 or saturated *para*-hydroxybenzyl substituted thiazolidinedione 15, known in prior art, in the presence of a base (Scheme III), similar to as described above for nucleophilic attack of *p*-hydroxy benzaldehyde 8 to the above key intermediates 3, 5, 6, 10a and 10b (Scheme I). The reagents, solvents and reaction condition can be advantageously utilized.

The various novel intermediates 3, 5, 9, 13 and 14 described in the present invention may be converted to corresponding salts by procedures known in prior art. For example, with pyridine ring in these intermediates, they can be converted to acid addition salts with acids such as hydrogen bromide, oxalic acid, hydrogen chloride, sulfuric acid, acetic acid, piciric acid, *p*-tolune sulfonic acid, maleic acid, methane sulfonic acid, benzenesulfonic acid, etc. Many of these salts are solids and offer operational simplicity for purification and manufacturing. Similarly, thiazolidinediones in 9, 13 and 14 can be converted to their corresponding cationic salts such as sodium ion, potassium ion, calcium ion or an ammonium ion and the like.

The novel process to manufacture Pioglitazone described in the present invention has the following advantages:

1. Less no of steps (4-6), especially the route 2 to 9 to 13 to 1; or 2 to 9 to 13 to 14 to 1.
2. Describes several new and novel intermediates eg., 9, 13, 14, 3 and 6.
3. Involves operational simplicity, as most of the intermediates involved are solids.
4. Offers opportunity to make cationic and protic salts, which will offer further operational simplicity during manufacturing and purification.

5. Involves high yielding solution phase chemistry and mild reaction conditions.
6. Provides pure intermediates and final product.
7. The process avoids use of unpleasent smelling acrylate derivatives and various other drawbacks mentioned in prior art.
8. All the above factors contribute to the cost effectiveness of the process of this invention.

Dated this 15th day of July 2002

Signature

To,
The Controller of Patents,
The Patent Office,
at Mumbai.

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